REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-40 were pending in this application. With this amendment, Claims 36 and 37 have been canceled without prejudice, and Claims 28-35 have been amended to clarify what Applicants have always regarded as their invention.

Claims 28-35 and 38-40 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

1. Formal Matters

Applicants thank the Examiner for entering the Preliminary Amendments filed on December 6, 2002, March 14, 2002 and August 29, 2002 into the record. Applicants further thank the Examiner for entering the Information Disclosure Statement filed on October 28, 2002 and March 6, 2002 into the record.

2. Priority

The Examiner states that due to the excessive number of applications from which the present application claims benefit, priority cannot be determined.

The Examiner's attention is respectfully directed to the Preliminary Amendment filed on August 29, 2002, which states that the present application is "a continuation of, and claims priority under 35 U.S.C. §120 to, U.S. Application 09/946,374 filed 9/4/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/04342 filed 2/18/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, U.S. Application 09/403,297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. §119 to US Provisional Application 60/100,627 filed 9/16/1998."

As discussed below, Applicants rely on the chondrocyte proliferation assay

(Example 153, Assay #111) for patentable utility which was first disclosed in PCT Application PCT/US00/04342 filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the February 18, 2000 priority. In support, Applicants enclose herewith page 525 of the PCT Publication WO 00/78961, corresponding to PCT Application PCT/US00/04342.

3. Information Disclosure Statement

In response to the Examiner's assertion that references 1 and 2 in the Information Disclosure Statement filed on October 28, 2002 are not in proper format, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

4. Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

5. Claim Objections

Claims 28-40 were objected to for reciting a Figure number and a SEQ ID NO. Applicants submit that the cancellation of Claims 36 and 37 renders the objection to these claims moot. Further, Applicants submit that Claims 28-35 have been amended to only recite SEQ ID NO. Accordingly, Applicants respectfully request that the Examiner withdraw its objection to Claims 28-35 and 38-40.

6. **Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)**

A. Claims 28-40 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner specifically notes that "the deposit of the biological material is considered necessary for the enablement of the current invention."

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

In response, Applicants enclose herewith a copy of the deposit receipt indicating that DNA64950-1590 deposit, ATCC Deposit No. 203224, was made by Applicants on September 15, 1998.

In addition, Applicants respectfully submit that the specification clearly discloses that the deposit was made under the Budapest Treaty and clearly provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and address of the depository starting on page 517, line 1 of the specification.

Applicants further submit that the specification has been amended to recite that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

B. The Examiner further alleges that even if a deposit is made under the terms of the Budapest Treaty, which Applicants assert they do, "claims 28-40 would still be rejected under 35 U.S.C. §112, first paragraph, because the specification, while then being enabling for SEQ ID NO:147 and 148, does not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:148, to the protein encoded by ATCC

No. 203224, for the extracellular domain thereof, or for fusion proteins." In addition, the Examiner alleges that "[t]he claims are broad ... because the claims have no functional limitation."

Applicants respectfully disagree and traverse the rejection.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite a functional limitation wherein the claimed polypeptide "induces chondrocyte proliferation." Applicants submit that the specification provides ample enablement for such polypeptides based on the *in vitro* data provided in the chondrocyte proliferation example (Example 153). Coupled with the general knowledge in the art at the time of the invention, Applicants submit that the present application provides sufficient guidance to one skilled in the art to use the invention without undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. The Examiner is therefore, respectfully requested to reconsider and withdraw the rejection of these claims under 35 U.S.C. §112, first paragraph.

7. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-40 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner notes that "[t]he claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:148 [without requiring] that the polypeptide of the present invention possess any particular biological activity . . . ."

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these

claims moot.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit that amended Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation that the polypeptide induces chondrocyte proliferation. Accordingly, it is no longer true that the claims are drawn to a genus of polypeptides defined by sequence identity alone. Therefore, the recited biological activity, coupled with a well defined, and relatively high degree of sequence identity is believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

8. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 28-40 are rejected under 35 U.S.C. §112, second paragraph, for allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner notes that PRO1347 is "a soluble protein" and is not "disclosed as being expressed on a cell surface." Accordingly, the Examiner asserts that the recitation of "extracellular domain" and the recitation of "the extracellular domain ... lacking its associated signal sequence" are indefinite.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot. Further, terms "extracellular domain" and "extracellular domain ... lacking its associated signal sequence" are no longer present in Claims 28-33 (and, as a consequence, those claims dependent from the same). Accordingly, Applicants request that the rejection of Claims 28-35 or 38-40 under 35 U.S.C. §112, second paragraph, be withdrawn.

9. Closest Prior Art

Applicants respectfully submit that Shibui *et al.* is not prior art.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for an extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2830 P1C11**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 6, 2004

By: _____
Anna L. Barry (Reg. No. 51,436)

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Genentech, Inc.
Attn: Ginger R. Dreger
1 DNA Way
South San Francisco, CA 94080-4990

Deposited on Behalf of: Genentech, Inc.

Identification Reference by Depositor:	**ATCC Designation**
pRK5E-based plasmid DNA64952-1568 (Ref. PR1568)	203222
pINCY-based plasmid DNA64903-1553 (Ref. PR1553)	203223
pRK5D-based plasmid DNA64950-1590 (Ref. PR1590)	203224
pINCY-based plasmid DNA66521-1583 (Ref. PR1583)	203225
pBlue-based plasmid DNA66520-1536 (Ref. PR1536)	203226
pRK5B-based plasmid DNA65423-1595 (Ref. PR1595)	203227

The deposits were accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above. The deposits were received September 15, 1998 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will not inform you of requests for the strains.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested October 2, 1998 On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: October 7, 1998

EXAMPLE 152: Proliferation of Rat Utricular Supporting Cells (Assay 54)

This assay shows that certain polypeptides of the invention act as potent mitogens for inner ear supporting cells which are auditory hair cell progenitors and, therefore, are useful for inducing the regeneration of auditory hair cells and treating hearing loss in mammals. The assay is performed as follows. Rat UEC-4 utricular epithelial cells are aliquoted into 96 well plates with a density of 3000 cells/well in 200 μl of serum-containing medium at 33°C. The cells are cultured overnight and are then switched to serum-free medium at 37°C. Various dilutions of PRO polypeptides (or nothing for a control) are then added to the cultures and the cells are incubated for 24 hours. After the 24 hour incubation, ^{3}H-thymidine (1 μCi/well) is added and the cells are then cultured for an additional 24 hours. The cultures are then washed to remove unincorporated radiolabel, the cells harvested and Cpm per well determined. Cpm of at least 30% or greater in the PRO polypeptide treated cultures as compared to the control cultures is considered a positive in the assay.

The following polypeptides tested positive in this assay: PRO1340.

EXAMPLE 153: Chondrocyte Proliferation Assay (Assay 111)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce the proliferation and/or redifferentiation of chondrocytes in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of the metacarpophalangeal joint of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm^2 in Ham F-12 containing 10% FBS and 4 μg/ml gentamycin. The culture media is changed every third day and the cells are reseeded to 25,000 cells/cm^2 every five days. On day 12, the cells are seeded in 96 well plates at 5,000 cells/well in 100μl of the same media without serum and 100 μl of either serum-free medium (negative control), staurosporin (final concentration of 5 nM; positive control) or the test PRO polypeptide are added to give a final volume of 200 μl/well. After 5 days at 37°C, 20 μl of Alamar blue is added to each well and the plates are incubated for an additional 3 hours at 37°C. The fluorescence is then measured in each well (Ex:530 nm; Em: 590 nm). The fluorescence of a plate containing 200 μl of the serum-free medium is measured to obtain the background. A positive result in the assay is obtained when the fluorescence of the PRO polypeptide treated sample is more like that of the positive control than the negative control.

The following PRO polypeptides tested positive in this assay: PRO1265, PRO1412, PRO1347, PRO1279, PRO1410 and PRO1474.

EXAMPLE 154: Inhibition of Heart Neonatal Hypertrophy Induced by LIF+ET-1 (Assay 74)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to inhibit neonatal heart hypertrophy induced by LIF and endothelin-1 (ET-1). A test compound that provides a positive response in the present assay would be useful for the therapeutic treatment of cardiac insufficiency diseases or disorders characterized or associated with an undesired hypertrophy of the cardiac muscle.

Cardiac myocytes from 1-day old Harlan Sprague Dawley rats (180 μl at 7.5 x 10^4/ml, serum <0.1, freshly isolated) are introduced on day 1 to 96-well plates previously coated with DMEM/F12 + 4%FCS. Test